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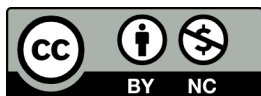
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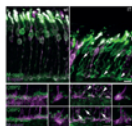
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Atrial myocytes demonstrate the diversity of cardiac calcium signalling

Comment on: Hohendanner F, et al. Cytosolic and nuclear calcium signaling in atrial myocytes: IP₃-mediated calcium release and the role of mitochondria. Channels 2015; 9(3):129–38; PMID: 25891132; <http://dx.doi.org/10.1080/19336950.2015.1040966>

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Atrial myocytes show a wider diversity of physiological calcium (Ca²⁺) signals than their ventricular counterparts. A study by Hohendanner and colleagues¹ examines the fine tuning of Ca²⁺ signals within atrial myocytes.

Beating mammalian hearts require the repetitive firing of action potentials from the pace-making sino-atrial node, and the coordinated contraction and relaxation of many millions of cardiac myocytes as action potentials sweep through the atrial and ventricular chambers. When an action potential reaches a myocyte within the atrial or ventricular chambers it causes their cell membrane (the sarcolemma) to depolarise, and thereby triggers a rapid, transient, Ca²⁺ signal. Subsequently, the Ca²⁺ signal causes the actin and myosin fibres to engage, and thus elicits myocyte contraction.²

The depolarisation-evoked Ca²⁺ signals are caused by the interplay of different types of Ca²⁺ channels. Specifically, sarcolemmal depolarisation triggers voltage-activated Ca²⁺ channels, allowing Ca²⁺ to enter from the external medium. This Ca²⁺ entry triggers the opening of other Ca²⁺ channels known as ryanodine receptors (RyRs), which sit on the sarcoplasmic reticulum, by a process known as Ca²⁺-induced Ca²⁺ release (CICR).

Action potentials cause both atrial and ventricular myocytes to contract by evoking sarcolemmal depolarisation and Ca²⁺ signals, but with differences. Mammalian ventricular myocytes respond to an action potential with a Ca²⁺ signal that arises simultaneously across the whole cell. With atrial myocytes from many mammalian species action potential-evoked Ca²⁺ signals are not simultaneous,

whole-cell events. Rather, they occur as Ca²⁺ waves that arise at the edge of a myocyte and propagate in a centripetal manner inside the cell³. A critical difference between ventricular and atrial myocytes is that the former cells have distinctive thin (100 – 200 nm) sarcolemma invaginations called transverse tubules (T-tubules) that convey action potentials deep into the cells.⁴

In terms of T-tubule expression, mammalian atrial myocytes are much more diverse than their ventricular counterparts. Some species express extensive T-tubules in their atrial cells. Whereas, others have no T-tubules, a few dispersed T-tubules, or a less organised series of sarcolemma invaginations that run transversely and axially.⁵ In those atrial myocytes that do not have sarcolemma invaginations, action potential-evoked Ca²⁺ signals will solely arise at the edge of the cells and propagate inwards. So, to understand the regulation of atrial contraction, it is important to determine what controls the propagation of centripetal Ca²⁺ waves.

Hohendanner et al. used rabbit atrial myocytes, which do not express T-tubules and therefore rely entirely on centripetal Ca²⁺ waves. They observed that centripetal Ca²⁺ wave propagation was faster at the cell periphery than in the cell centre. This two-speed Ca²⁺ wave propagation was due to mitochondria (Fig. 1). By sequestering Ca²⁺, mitochondria dampen CICR and inhibit Ca²⁺ wave propagation. Their observations provoke a number of intriguing questions; what purpose would mitochondrial Ca²⁺ uptake serve? Why dampen the propagation of a Ca²⁺ wave when it is needed to trigger contraction?

Firstly, mitochondrial respiration is regulated by the concentration of Ca²⁺ within the mitochondrial matrix. So, by sequestering Ca²⁺ mitochondria can match cellular activity and energy production. Secondly, the ventricular chambers, which are larger and stronger muscles, are responsible for the bulk of blood pumping. The atrial chambers enhance the filling of ventricular chambers with blood, and are particularly important during periods of exercise. It has been demonstrated that the extent of the inward centripetal Ca²⁺ wave propagation modulates the contraction of atrial myocytes. So, by dampening Ca²⁺ wave propagation, mitochondria serve to limit contraction, and conserve energy, when forceful contraction is not needed, but their dampening effect must be overcome when stronger contraction is required.

One way in which the dampening effect of mitochondrial Ca²⁺ uptake can be overcome is to activate additional Ca²⁺ channels during Ca²⁺ wave propagation. Hohendanner et al demonstrated that inositol 1,4,5-trisphosphate receptors (InsP₃Rs) augment Ca²⁺ signalling within atrial myocytes. To trigger the specific opening of InsP₃Rs, Hohendanner et al used photolytic uncaging of InsP₃. They found that depolarisation-evoked Ca²⁺ transients were larger following uncaging of InsP₃ inside an atrial myocyte. In essence, InsP₃Rs act to boost CICR as a Ca²⁺ wave passes by.

Although InsP₃ enhanced centripetal Ca²⁺ wave propagation in atrial myocytes, uncaging InsP₃ did not trigger Ca²⁺ waves by itself unless mitochondrial Ca²⁺ uptake was blocked. This observation alludes to another function of mitochondrial Ca²⁺ uptake;

preventing arrhythmic Ca^{2+} signals. As described earlier, a beating heart requires the coordinated activation of Ca^{2+} release following myocyte depolarisation. However, InsP_3Rs

can activate solely upon the binding of InsP_3 , and unlike RyRs don't have to wait for cellular depolarisation to trigger CICR. InsP_3Rs can therefore release Ca^{2+} during periods when a myocyte should be silent. Promiscuous Ca^{2+} release in the heart is dangerous, as it disrupts myocyte beating⁶. Atrial myocytes use InsP_3Rs as a means to boost Ca^{2+} signals and thereby enhance contraction, but need mitochondrial Ca^{2+} uptake to prevent InsP_3Rs from triggering arrhythmic Ca^{2+} waves.

The responses to uncaging of InsP_3 observed by Hohendanner *et al* were not the same throughout an atrial myocyte. The nucleus was more responsive to InsP_3 than the remainder of the cell. Uncaging InsP_3 evoked mini Ca^{2+} waves that were restricted to the nucleus. This nuclear restriction was also due to the Ca^{2+} uptake by mitochondria. InsP_3 is highly diffusible inside cells and can pass through nuclear pore complexes, thereby triggering nucleoplasmic Ca^{2+} signals. Any Ca^{2+} escaping through nuclear pores would be sequestered by perinuclear mitochondria, thus making the nucleus an autonomous Ca^{2+} signalling domain. It is likely that nuclear Ca^{2+} signals caused by InsP_3Rs will modulate myocyte gene expression, and that the particular genes will be different to those affected by the centripetal Ca^{2+} waves that also invade the nucleoplasm.

Atrial myocytes are amazing cells in which to study Ca^{2+} signalling because of their ability to show diverse responses. Their regular structure and geometry belies a Ca^{2+} signalling toolkit with multiple interacting components to enable discrete subcellular and whole-cell Ca^{2+} signals that are highly plastic and suit particular physiological needs.

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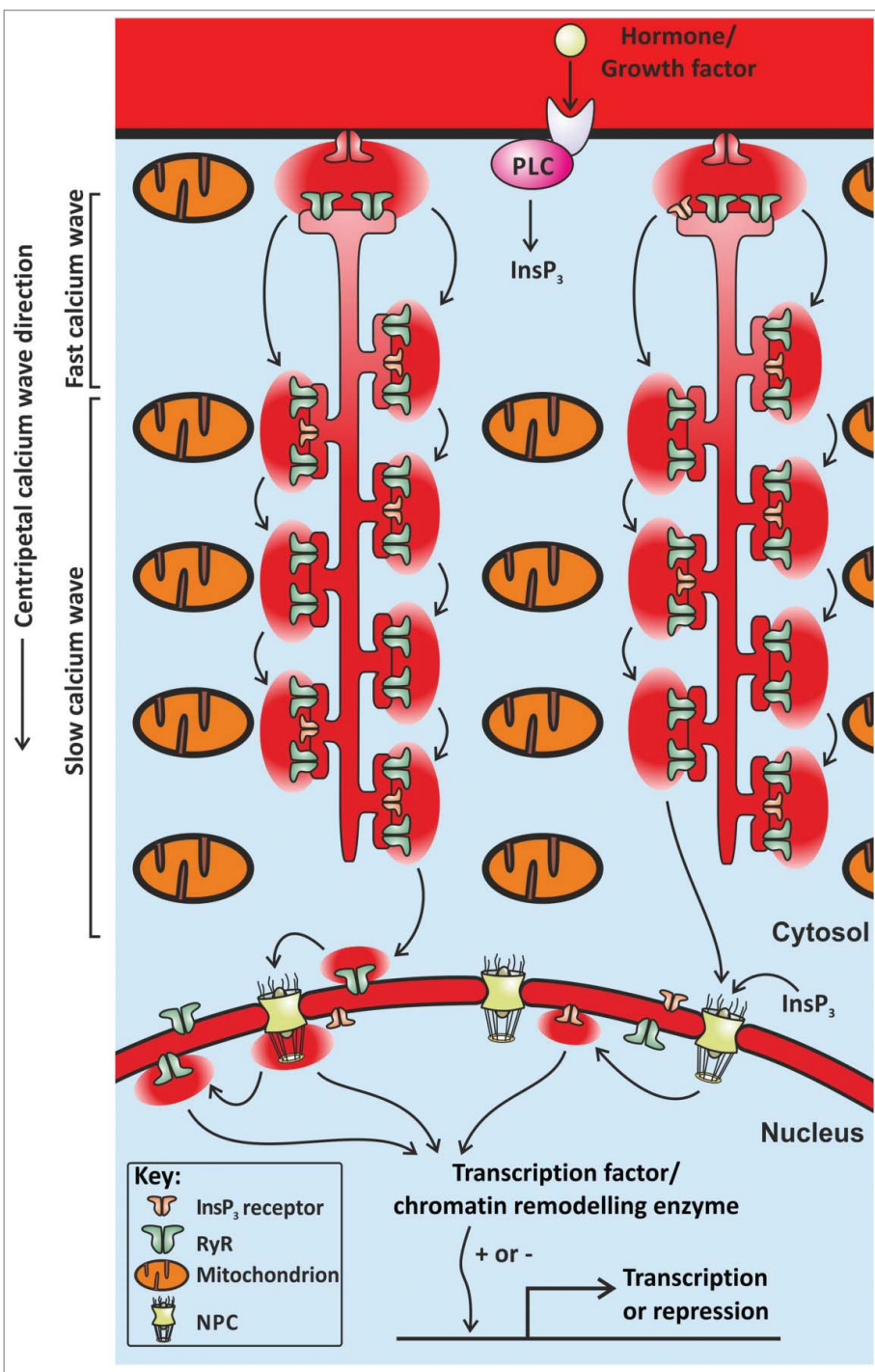


Figure 1. The Figure shows an illustration of part of an atrial myocyte. The arrows denote the movement of Ca^{2+} ions as a centripetal wave. The Ca^{2+} wave propagates via CICR between neighbouring clusters of RyRs. In the presence of InsP_3 , Ca^{2+} wave propagation is boosted by the opening of InsP_3Rs . Both Ca^{2+} and InsP_3 can pass through nuclear pore complexes (NPC), and trigger nucleoplasmic Ca^{2+} signals that influence gene transcription. Mitochondria sequester Ca^{2+} ions, and thereby retard Ca^{2+} wave propagation.